## Synaptic dysregulation in a human iPS cell model of mental disorders.

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**Public Summary:**
Dysregulated neurodevelopment with altered structural and functional connectivity is believed to underlie many neuropsychiatric disorders, and 'a disease of synapses' is the major hypothesis for the biological basis of schizophrenia. Although this hypothesis has gained indirect support from human post-mortem brain analyses and genetic studies, little is known about the pathophysiology of synapses in patient neurons and how susceptibility genes for mental disorders could lead to synaptic deficits in humans. Genetics of most psychiatric disorders are extremely complex due to multiple susceptibility variants with low penetrance and variable phenotypes. Rare, multiply affected, large families in which a single genetic locus is probably responsible for conferring susceptibility have proven invaluable for the study of complex disorders. Here we generated induced pluripotent stem (iPS) cells from four members of a family in which a frameshift mutation of disrupted in schizophrenia 1 (DISC1) co-segregated with major psychiatric disorders and we further produced different isogenic iPS cell lines via gene editing. We showed that mutant DISC1 causes synaptic vesicle release deficits in iPS-cell-derived forebrain neurons. Mutant DISC1 depletes wild-type DISC1 protein and, furthermore, dysregulates expression of many genes related to synapses and psychiatric disorders in human forebrain neurons. Our study reveals that a psychiatric disorder relevant mutation causes synapse deficits and transcriptional dysregulation in human neurons and our findings provide new insight into the molecular and synaptic etiopathology of psychiatric disorders.

**Scientific Abstract:**
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